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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,477	LORINCZ ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0505*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on May 18, 2005 has been entered.

Claims 8-12 have been amended and claims 13-22 have been added. Claims 8-22 are now pending and under consideration.

Specification

2. The amendment filed June 13, 2003 remains objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. It is noted that while applicant has amended the specification so as to overcome in part the prior objection set forth in the Final Rejection mailed April 19, 2004, applicant's amendment of May 18, 2005 retains the recitation on page 23, at line 20, of the language "to calibrators and cellular RNA."

35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is on page 23, at line 20: the insertion of the language "to calibrators and cellular RNA." While the specification previously indicated that probe mix was "added and hybridized" to "RNA specimens" earlier referred to as "Aliquots of cellular RNA," the specification as amended indicates that probe mix was added and hybridized to both

cellular RNA and "calibrators." As the originally filed specification did not specifically refer to these steps being taken with the "calibrators," this amendment also introduces new matter. In response to the earlier rejection of this language, Applicant (in the Remarks of May 18, 2005) argues that page 22, lines 1-3 and page 23, lines 15-21, provide support for the amendment. However, page 22, lines 1-3 is a discussion of a step performed in Example 3, while the objection pertains to steps taken during a different example, Example 4. Thus, the recitation at page 22, lines 1-3, cannot provide basis for modifying the method steps of Example 4 (it is noted that Example 4 does not, e.g., refer back to Example 3, indicate that particular steps of Example 3 are repeated, etc.). Regarding page 23, lines 15-21, it is noted that this is the text containing the amendment in question. This portion of the specification as originally filed did not specifically disclose the addition of probe mix to calibrators; rather, the specification stated: "Aliquots of cellular RNA were diluted to 50 ul and then 50 ul of Probe mix....was added and hybridized to the RNA specimens for 2 hours at 65 °C." While it is acknowledged that the recitation "RNA specimens" might be interpreted as encompassing specimens other than the previously recited "aliquots of cellular RNA," the specification does not in fact state that Probe mix was added to calibrators, and modifying the specification to provide more specific and detailed guidance than it originally provided constitutes the addition of new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Declaration under 37 CFR 1.132

3. The Declaration under 37 CFR 1.132 filed May 18, 2005 is sufficient to overcome the rejection of claims 8-12 under 35 USC 112, first paragraph for lack of enablement **in part**, as specified below (see discussion following the enablement rejection set forth below). With regard to newly added claims 13-22, said Declaration is insufficient to preclude the rejection of these claims under 35 USC 112, first paragraph for lack of enablement, for reasons discussed below.

Claim Rejections - 35 USC § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 8-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons stated in the Office action of April 19, 2004.

It is noted that the Declaration under 35 USC 1.132 filed May 18, 2005 is sufficient to overcome the instant rejection in part. Particularly, Applicant has established via the Declaration that HaCaT cells infected by the procedure of White et al are considered by those of skill in the art to be a model for early stage HPV16 infection (see, e.g., pp. 3-4 of the Declaration and p. 962 of White et al), that W12 cells (containing approximately 100 episomal copies of HPV16 DNA) are considered by those of skill in the art to be a model for low grade HPV16 induced lesions (see, e.g., p.

4 of the Declaration and p. 855 of Rong et al), and that SiHa cells (containing one integrated copy of HPV16 DNA) are considered to be a model for high grade HPV16-induced lesions (see, e.g., pp. 4-5 of the Declaration and p. 855 of Rong et al). Accordingly, Applicant's Declaration establishes enablement of the claims in part, specifically, to the extent that the claims are drawn to diagnosis of HPV16-induced cancer and stages thereof by detecting in patients the ratios encompassed by the instant claims.

However, the present claims are not limited to such methods, but rather encompass either any HPV type (claim 8) or any "high risk" HPV type (claims 9-12). While the Declaration does cite teachings in the art that E6 and E7 expression are associated with malignant transformation in cancers induced by other HPV types (citing, e.g., Koromilas et al and Goodwin and DiMaio), such teachings are insufficient to establish that the transcript ratios of the instant claims relate to particular types or stages of disease. Rather, such teachings (like those of Stoler et al, previously cited [Human Pathology 23(2):117-128 (2/1992)]), merely establish the fact that E6/E7 expression is often elevated in HPV-induced cancers. It is again noted that Stoler et al teach that the types and quantities of HPV transcripts expressed in patients vary depending on cancer type, HPV type, and cell/tissue location (p. 119-120). While Applicant's Declaration does establish a correlation between human disease and cultured cells comprising HPV16 nucleic acids, none of the cited references refute the teachings of the art exemplified by Stoler et al, which suggest that it is unpredictable as to whether ratios associated with HPV16-induced disease would be associated with

disease induced by other types of HPV. With particular regard to two references newly cited by Declarant in paragraphs 41-42 of the Declaration, it is noted that both the Stoler reference (Exhibit 16) and the Chow and Broker reference are silent with regard to ratios and/or with regard to correlations between HPV16 gene expression ratios and those of other "high risk" HPV types.

The Declaration also states Declarant's opinion that the claims are enabled, which opinion is supported by data and findings of E6-E7/L1 transcript ratios for HPV 18 in HeLa cells (pages 7-9) and HPV 31 in LKP31 and A31 cells (pages 10-12). Declarant reports an E6-E7/L1 mRNA ratio of 9.5 for HeLa cells (an HPV 18 positive human cervical carcinoma cell line), and states that "This E6-E7/L1 mRNA ratio correlates to the claimed invention, i.e. This ratio represents substantially higher expression of the carcinogenesis-related genes E6-E7 than the viral capsid structural L1 gene." Regarding data obtained with HPV 31, Declarant states that "Both cell lines utilized....LKP31 and A31, contained episomal and integrated copies of HPV 31 DNA; however, LKP31 had a higher copy number than A31, and thus LKP31 is assumed to represent a cell line that is closer to cancer" (see pages 10-11). Declarant reports an E6-E7/L1 ratio of 11.7 for the LKP31 cell line and 8.4 for the A31 cell line, stating that "The E6-E7/L1 mRNA ratio was found to be above 2 for both HPV 31 positive cell lines" and that "The levels of E6-E7 and L1 mRNA were approximately 2-fold higher in LKP31 cells than in the A31 cells." Declarant further states that "The higher level of E6-E7 to L1 is expected in cells that are transformed by HPV 31 to the pre-malignant state, and as expected, the more neoplastic cell line LKP31 has a higher ratio," and concludes that

"These experiments demonstrate that HPV gene transcript ratios of different HPV types, i.e., HPV 18 and HPV 31, may be used to determine the disease level in cell model systems of HPV-infected cells."

Declarant's opinions and data obtained with HPV 18 and HPV 31 are not persuasive with respect to enablement of the invention of the instant claims. First, it is noted that while the instant claims are limited to diagnostic methods employing patient samples, the data reported by Declarant was obtained with cultured cells. While, as discussed above, the Declaration does establish the validity of the 3 cell lines exemplified in the specification as models of various HPV 16-induced disease stages, neither the specification, the Declaration, nor the prior art establish a correlation between transcript ratios in HeLa cells and patients with a particular stage of HPV 18 induced disease, or between transcript ratios in LKP31 and/or A31 cells and patients with particular stages of HPV 31-induced disease. With further regard to HPV 18, the Declaration does not indicate with which of the three types/stages of disease disclosed in the specification the HeLa cell model is believed to correlate, or provide evidence of such a correlation. Thus, while the Declaration does provide evidence of a ratio of 9.5 for HeLa cells, it is unpredictable whether such a ratio might also be identified in a patient sample, and if detected, with what disease stage this ratio would correlate. With further regard to HPV 31, the Declaration similarly does not indicate with which of the three types/stages of disease disclosed in the specification the LKP31 and A31 cell models are believed to correlate. While Declarant does indicate that LKP31 is "assumed to represent a cell line that is closer to cancer" due to its higher HPV 31 copy

number, the Declaration does not indicate whether one or both of these cell lines represents cancer, a pre-malignancy, etc. It is further noted that these two cell lines are disclosed to be structurally different from the HPV 16 models of the specification; specifically, while both LKP31 and A31 contain both episomal and integrated copies of HPV 31 DNA, the SiHa cells of the specification contain 1-2 copies of integrated HPV 16 DNA and are disclosed to "represent cancer," while the W12 cells of the specification contain "approximately 100 copies of episomal HPV16 DNA" and are disclosed to represent "pre-malignant, immortalized cells or CIN II or CIN III." It is not apparent how or whether the LKP31 and A31 models relate either to different stages of HPV 31 induced disease, or to the HPV 16 models of the specification. While the Declaration does provide evidence of a ratio of 11.7 for LKP31 cells and of 8.4 for A31 cells, it is unpredictable whether such ratios might also be identified in a patient sample, and if detected, with what disease stage or stages these ratios would correlate. Finally, it is noted that while Declarant states that "HPV gene transcript ratios of different HPV types, i.e., HPV 18 and HPV 31, may be used to determine the disease level in cell model systems of HPV-infected cells," the instant claims are not drawn to the determination of disease levels in cell model systems, but the diagnosis of disease and disease stages in patients. Declarant's statements in paragraph 5 (page 2) that "For the experiments described, *in vitro* results are generally correlative with *in vivo* results" and that "Moreover, *in vitro* data are routinely used by those in the art who apply and extrapolate the findings and outcomes of in vitro cell culture experiments to *in vivo* use" are also noted. However, as Declarant has provided no actual evidence of such

correlations, nor examples of, e.g., references in which skilled artisans have shown such correlations or even stated that such correlations are known to exist, these arguments are not persuasive.

With regard to Applicant's arguments in the "Remarks" of May 18, 2005, it is again acknowledged (as discussed above) that the teachings of the specification in combination with the evidence provided in the Declaration of May 18, 2005 are sufficient to establish the validity of the cell culture models in the specification as being representative of HPV-16 induced diseases in patients, and therefore to enable the claims to the extent that they are drawn to diagnosis, etc., of HPV-16 induced cancer, stages, etc. in patients. Further, the examiner does not dispute Applicant's statement that "there is strong correlation between HPV infection and human disease." However, the instant claims are drawn to methods in which specific, particular ratios of mRNAs are detected in patients as indicators of disease. Applicant has provided no evidence of a correlation between the data presented in the specification and disease induced by any HPV type other than HPV16. Applicant's specification as filed contained no data of any kind with respect to HPV types other than HPV16, and (as discussed above) the Declaration of May 18, 2005 describes experiments conducted with different HPV types and different *in vitro* models than those employed in the specification. As discussed above, those data do not support enablement of the claims of record. While Applicant's arguments are further persuasive with regard to the enablement of the invention as drawn to HPV16, it is completely unpredictable as to whether any quantity of experimentation would be sufficient to allow one of skill to practice the claimed invention

with regard to any other HPV type. It is noted that several of the claims have been amended to recite "high risk" HPV types, and Applicant's arguments with regard to the disclosure of a "representative number" of species are also acknowledged. However, Applicant's attention is again drawn to the claims, and to the fact that the claims require the detection of particular ratios (not merely, e.g., elevation of a particular transcript) as an indicator of disease. Applicant has not demonstrated, e.g., that two or three high risk HPV types exhibit similar ratios in the same or correlating cell culture models, which models are known to correlate with particular disease stages in patients. Rather, Applicant has provided persuasive evidence that their invention is enabled for a single high-risk HPV type, HPV16. Evidence that HPV16 is in fact representative of high-risk HPV within the context of the claimed invention is lacking. Accordingly, Applicant's Declaration and arguments, considered in combination with the other evidence available to the examiner (including the teachings of the specification and of the prior art), are ineffective to establish enablement of the claimed invention with respect to HPV 18, HPV 31, or other HPV types other than HPV 16 at the time the invention was made.

6. Claims 13-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These

factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (MPEP 2164.01(a)).

Claims 13, 15, and 16 are drawn to methods of "diagnosing risk of HPV18-induced neoplasia by detecting HPV18-induced cell transformation in a patient infected with HPV" (claim 13), methods of "diagnosing stage of HPV18-induced disease in a patient infected with HPV18" (claim 15), and methods of "diagnosing HPV18-induced cancer in a patient infected with HPV18" (claim 16). In these methods, the ratio of E6 and/or E7 mRNA level to L1 and/or L2 and/or E2 mRNA level is determined, and a ratio of greater than 2 is indicative of "HPV18-induced cell transformation and risk of neoplasia" (claim 13) or "early stage HPV18-induced disease" (claim 15), while a ratio of greater than 4 is indicative of "HPV18-induced cancer" (claim 16). Claims 14 and 17 are drawn to methods "of diagnosing the onset of HPV18-induced neoplasia in a patient infected with HPV18" (claim 14) and methods "of diagnosing the risk or onset of HPV18-induced cancer in a patient infected with HPV18" (claim 17). In these methods, the ratio of group I mRNA level to group II and/or group III mRNA level is determined, and a ratio of greater than 2 is indicative of "HPV18-induced neoplastic onset" (claim 14), while a ratio of greater than 4 is indicative of "high risk or onset of HPV18-induced cancer" (claim 17). Claims 18, 20, and 21 are drawn to methods of "diagnosing risk of HPV31-

induced neoplasia by detecting HPV31-induced cell transformation in a patient infected with HPV" (claim 18), methods of "diagnosing stage of HPV31-induced disease in a patient infected with HPV31" (claim 20), and methods of "diagnosing HPV31-induced cancer in a patient infected with HPV31" (claim 21). In these methods, the ratio of E6 and/or E7 mRNA level to L1 and/or L2 and/or E2 mRNA level is determined, and a ratio of greater than 2 is indicative of "HPV31-induced cell transformation and risk of neoplasia" (claim 18) or "early stage HPV31-induced disease" (claim 20), while a ratio of greater than 4 is indicative of "HPV31-induced cancer" (claim 21). Claims 19 and 22 are drawn to methods "of diagnosing the onset of HPV31-induced neoplasia in a patient infected with HPV31" (claim 19) and methods "of diagnosing the risk or onset of HPV31-induced cancer in a patient infected with HPV31" (claim 22). In these methods, the ratio of group I mRNA level to group II and/or group III mRNA level is determined, and a ratio of greater than 2 is indicative of "HPV31-induced neoplastic onset" (claim 19), while a ratio of greater than 4 is indicative of "high risk or onset of HPV31-induced cancer" (claim 22). The specification indicates that group I genes include E6, E7, and E6 + E7, that group II genes include L1, L2, E4, and combinations thereof, and that group III includes E1, E2, E5, and combinations thereof (specification p. 10).

The specification exemplifies quantitation of HPV16 mRNA in different cultured cell lines (Example 1-2, Example 4). Cell lines examined include HaCaT cells, SiHa cells, and W12 cells. The specification teaches that HaCaT cells are an "immortalized human keratinocyte cell line" comprising approximately 1 episomal copy of HPV16 for every 40 cells, and states that "These cells are considered a representative of early

stage infection or CIN I (cervical intraepithelial neoplasia)" (p. 22-23). The specification teaches that SiHa cells are a "human cancer cell line" containing "1-2 copies of HPV16 integrated into the genome", and states that "These cells are considered to represent cancer" (p. 22-23). The specification teaches that W12 cells are a "non-tumorigenic human cervical keratinocyte cell line" that "contain approximately 100 copies of episomal HPV16 DNA and represent pre-malignant, immortalized cells or CIN II or CIN III" (p. 22-23).

The teachings of the specification show that the HPV16 (E6+E7)/L1 mRNA ratio is 0.68 for "early stage infection" HaCaT cells, 4.00 for "pre-malignant, immortalized" W12 cells, and "infinitely large" for "malignant" SiHa cells (p. 24, Table 2). Thus, based on the teachings of the specification, it appears that one of skill in the art could distinguish these three cell culture models of infection from one another by determining the HPV16 (E6+E7)/L1 gene transcript ratio. While the specification indicates that other ratios of HPV16 gene transcripts were measured and calculated for W12 and SiHa cells, no other data is presented for HaCaT cells (Table 2). However, with respect to W12 and SiHa cells, Applicant further demonstrates that these two cell types have different HPV16 mRNA ratios for 5 other transcript combinations (see Table 2).

It is unpredictable as to whether one of skill in the art could practice the claimed invention. The instant claims are directed to methods of, e.g., diagnosing cancer, cancer risk, or neoplastic onset in a patient, and are limited to disease caused by HPV18 (claims 13-17) or HPV31 (claims 18-22). First, the specification does not provide evidence that the HPV gene transcript ratios set forth in the claims are

associated with transformation, cancer, disease stage, etc., in a patient. The data presented in the specification are limited to HPV16 transcript ratios in different types of cultured cell models, as discussed above. It is noted that Applicants have now provided declaratory evidence (see Declaration of May 18, 2005 and the discussion above) that establishes the validity of the various types of cultured cells employed in the specification as disease models for disease caused by HPV16. However, neither the specification nor the Declaration provide evidence of the enablement of the invention of instant claims 13-22 at the time the instant invention was made (see discussion above). Further, the prior art is silent with respect to a correlation or correspondence between HPV16 gene transcript ratios measured in the 3 particular cell culture models employed by applicants and ratios of HPV18 and/or HPV31 transcripts measured either in these same cell culture models or in samples from patients. Further, with regard to the HPV18 and HPV31 data presented in the Declaration of May 18, 2005, Applicant has similarly not provided evidence of a correlation between the cell culture models of the Declaration and those originally described in the specification, or between the cell culture models of the Declaration and findings in patients. Additionally, it is noted that the specification as originally filed provided no evidence of any kind obtained with either HPV18 or HPV31; Applicant is reminded that 35 USC 112, first paragraph requires enablement of an invention as of the filing date of an application (see, e.g., MPEP 2164.01). The prior art as exemplified by Stoler et al (Human Pathology 23(2):117-128 [2/1992]) does suggest that expression of HPV E6 and E7 genes is elevated in some types of cancers (see entire reference). For example, Stoler et al demonstrate that, in

high-grade squamous intraepithelial lesions associated with HPV-16, "signals from the E6-E7 ORFs were equal to or higher than from those from the E4-E5 region", whereas in low-grade squamous intraepithelial lesions, "Probes for transcripts spanning the E4-E5 ORFs yielded the most intense signals" (p. 119). However, the claimed invention is limited to the detection of particular ratios of mRNA levels to accomplish diagnosis of HPV18 or HPV31 induced disease, and the prior art does not provide evidence that detection of the particular transcript ratios required by the instant claims would allow diagnosis in a patient of cancer, cancer risk, cancer stage, neoplastic onset, etc. Stoler et al also teach that the types and quantities of HPV transcripts expressed in patients will vary depending on cancer type, HPV type, and cell/tissue location (p. 119-120). Stoler et al further teach that HPV types 6 and 11, 16, and 18 are associated with different disease types (p. 117), and it is well known to those of skill in the art that different HPV types are associated with different disease types and cause diseases of varying severity. Thus, neither the specification nor the teachings of the prior art establish a correspondence or correlation between the particular ratios of HPV transcripts recited in the instant claims and HPV18 and/or HPV31 induced disease in a patient. As it is unknown as to whether such a correspondence or correlation exists, it is unpredictable as to whether any quantity of experimentation would be sufficient to allow one of skill in the art to use the claimed invention. In view of the lack of guidance in the specification and in the prior art with respect to diagnosis and/or monitoring of cancer in a patient by determination of the HPV gene transcript ratios of the claims, it would require undue experimentation to use the claimed invention.

To the extent that Applicant's Declaration and Remarks of May 18, 2005 are applicable to new claims 13-22 and to the instant rejection, the examiner's response to the Declaration and the Remarks set forth above applies equally herein.

Terminal Disclaimer

7. The terminal disclaimer filed on October 18, 2004 disclaiming the terminal portion of any patent granted on this application that would extend beyond the expiration date of US Patent No. 6,355,424 B1 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
Primary Examiner
Art Unit 1634
August 20, 2005